

Influence of pemphigoid gestationis on pregnancy outcome: A case report and review of the literature

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Abstract. Pemphigoid gestationis is considered to be a rare pregnancy exclusive bullous disease, which modifies the course of the pregnancy, with difficulties in the management of the pruritus and skin lesions as well as a possible change in the neonatal outcome. Differential diagnosis of skin lesions and pruritus in pregnancy is challenging, and complementary investigations such as skin biopsy or laboratory tests are indispensable. The correct diagnosis and proper treatment could change the natural course of a pregnancy at risk and could improve maternal and fetal morbidity. We present the case of a patient with pemphigoid gestationis with the aim to highlight: i) the management of this pregnancy-associated skin disorder which transfers this pregnancy into a category of high obstetrical risk pregnancy; ii) the particularities of the course of the pregnancy; and iii) the importance in the differential diagnosis of pregnancy dermatoses. The particularity of this case of pemphigoid gestationis was the acute fetal distress in the absence of intrauterine growth restriction that is frequently found in this pathology, and the management of a rare pregnancy skin condition that currently has no standard treatment.

Introduction

Pregnancy dermatoses represent a diverse group of mucocutaneous conditions characterized by pruritus and inflammation occurring only during pregnancy or immediately postpartum (1). The most frequent pathologies include atopic eruption of pregnancy, polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy (ICP), pustular psoriasis of pregnancy (PPP) and pemphigoid gestationis (PG). The moment of onset should be noted as there are conditions that occur earlier in pregnancy, such as atopic eruption of pregnancy, and conditions which complicate the second or third trimester of pregnancy or even the postpartum period (PG, PEP and ICP) (2).

PG, in the past known as herpes gestationis, represents an autoimmune bullous disease occurring exclusively after the second part of the pregnancy (3). PG is a rare disease, its incidence being 1 out of 20,000 to 50,000 pregnancies. Besides pregnancy, PG has been reported to appear in several cases of women with trophoblastic tumors as a paraneoplastic phenomenon (4-6).

The pathogenesis is based on the appearance of circulating IgG1 antibodies against the bullous pemphigoid antigen, known as BP180 or collagen XVII. This antigen is in fact a transmembrane hemidesmosomal glycoprotein, which contributes to the formation of the cutaneous basement membrane zone (7). In PG, the binding of IgG1 to BP180 creates an inflammatory cascade responsible for the detachment of the epidermis from the profound layer, the dermis (8). It appears that the placenta is the initial site of autoimmunity, as these IgG1 antibodies bind also to the amniotic and chorionic epithelia, in addition to the epidermal basement membrane zone, which all have ectodermal origin. One theory sustains the existence of paternal antigens from the second class of major histocompatibility complex on the chorionic villi, which generate an immune response from the mother, resulting in antibodies against the amniotic basement membrane. This theory suggests that these

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antibodies could cross-react with the variable antigens from the maternal skin and induce maternal and even fetal disease (9). Another hypothesis sustains a genetic predisposition, as there have been studies that have shown a possible interconnection between PG and second-class human leukocyte antigen (HLA), especially the phenotype HLA-DR3/HLA-DR4 (10).

Clinical manifestations of PG include extreme pruritus, papules and plaques which form tense blisters that typically appear periumbilical and spread to the trunk and extremities. The lesions usually spare the face and the mucous membranes. Although the symptoms may remit spontaneously before delivery, 75% of cases burst after delivery and 25% of cases burst monthly during menses or while using contraceptive pills. Usually, the majority of cases resolve automatically within the first weeks to several months postpartum. PG may reoccur in a more violent form with subsequent pregnancies, but it can also be absent (11).

Regarding neonatal outcome, PG is associated with a higher risk of premature delivery and, due to a moderate placental failure, women with PG deliver small-for-gestational-age fetuses. There have been no reports of an elevated risk of miscarriage (12). One study concluded that the obstetrical prognosis is influenced by the debut of PG and the existence of blisters on the patient's skin; an early debut in the first or second trimester announces an altered prognosis (13). Although there is not enough evidence to sustain a link between PG and an obscure prognosis, in another study Al-Saif *et al* reported the outcome of 32 patients with PG, from which 6 were preterm deliveries, 2 pregnancies presented intrauterine growth restriction and another 2 pregnancies finished with abortion or stillbirth (14). IgG autoantibodies could pass the placenta and induce neonatal PG which presents with minor symptoms and resolves spontaneously within weeks. Due to the maternal systemic treatment of the disease, adrenal suppression might occur in babies, but there is a minimum risk even if there were high-dose corticosteroids administered to the mother (15).

The diagnosis is based on the clinical symptoms and signs, skin biopsy with direct immunofluorescence (DIF) and serum level of BP180 antibodies using enzyme-linked immunosorbent assay (ELISA).

As there are few cases of PG, there is yet no standard treatment; the management is mostly based on the clinician's experience combined with the existing literature of bullous pemphigoid and with the collaboration of a dermatologist and a pathologist (16,17). The first recommendation is to use high-potency topical corticosteroids. The second treatment line is represented by systemic corticosteroids, such as prednisone 0.5 mg/kg daily, which appears to be effective. Postpartum, prednisone can be administered up to 2 mg/kg daily in severe cases. Other successful postpartum administered therapies include azathioprine, cyclosporine, doxycycline, high-dose intravenous immunoglobulins, cyclophosphamide, rituximab, nicotinamide and immunoadsorption. Oral antihistamines such as chlorpheniramine or loratadine could aid with the control of the pruritus (18,19).

In this article, we present the case of a pregnancy complicated with PG with the aim to highlight the difficulties in the differential diagnosis of pregnancy dermatoses, the management of this particular pathology and the importance of monitoring such a pregnancy with high obstetrical risk.

Case report

A 40-year-old woman presented to our obstetrics clinic, Life Memorial Hospital (Bucharest, Romania) one year before for early diagnosis and monitoring of a singleton pregnancy. From the gynecologic history, we noted a surgery for a benign condition 2 years prior complicated with an unspecified dermatitis immediately after. Her medical history included the presence of autoimmune thyroiditis. A noninvasive prenatal test was performed and the major chromosomal abnormalities were excluded. The course of the pregnancy was uneventful, and the ultrasound and paraclinical monitoring were normal. We noted nothing abnormal on the blood tests and the fetal growth was according to the gestational age, until the 30th week of pregnancy, when the patient presented with pruritus and papules on the abdomen. The patient was counseled to undergo a dermatologic consultation. The first clinical diagnosis was contact dermatitis and the patient received topical corticosteroids, which had a favorable effect on the remission of the pruritus and cutaneous lesions. After two weeks, the patient returned with generalized and intense pruritus and papules, which raised the suspicion of PG (Fig. 1). Topical corticosteroids administered this time were ineffective and at 35-weeks gestation she receives systemic corticosteroids consisting of 4 doses of 8 mg dexamethasone, as the severity of the symptoms was increasing and the pruritus became unbearable. The skin biopsy performed revealed superficial perivascular dermatitis with lymphocytes and eosinophils, with superficial perivascular lymphocytic and eosinophilic infiltrate and interstitial eosinophilic infiltrate, with some eosinophils in groups located subepidermal (Fig. 2). The direct immunofluorescence showed linear and continuous deposit of IgG and C3 in the dermoepidermal junction, with no IgA, IgM or C1q deposits (Fig. 3). The existence of a linear deposit of C3 in the dermoepidermal junction, more specifically at the basement membrane zone, is pathognomonic for PG. Anti BP180 antibodies were not performed, but the skin biopsy, along with the direct immunofluorescence and symptoms confirmed the diagnosis.

At 35 weeks of gestation, due to acute fetal distress, a male fetus of 2,900 g with an APGAR score at 1 min of 9 was delivered by Cesarean section. The fetus had a good adaptation and a normal neonatal period, without any pemphigoid lesions.

The patient had an exacerbation of the disease immediately postpartum (Fig. 4) and received topical and systemic corticosteroids, and the evolution of PG was favorable under treatment. The systemic corticosteroids were reduced to a minimum dose with a maximum effect on the remission of the disease. The patient was counseled to use sulphur soap, antihistaminic drugs, fusidic acid and sulfadiazinum for the skin lesions, but all of these increased the rash due to skin dryness; a general recommendation was to avoid ordinary laundry detergent and to replace it with another one for sensitive skin, with no perfume. Immediately postpartum, the patient received 64 mg of methylprednisolone daily and the dose was reduced gradually to a maintenance dose of 32 mg every two days at 3 months postpartum, that proved to be a minimum dose under which the pathology remained under control. The complete remission has not been achieved even 18 months after delivery.



Figure 1. Pemphigoid gestationis lesions occurring in the 32nd week of gestation: urticarial papules and plaques surrounding the umbilicus.

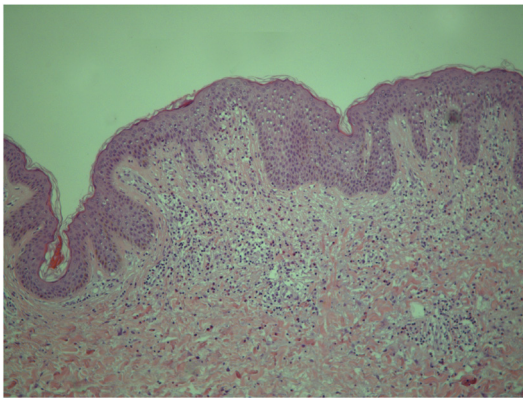


Figure 2. Hematoxylin and eosin (H&E) staining of the skin biopsy. Conventional H&E histopathological staining shows perivascular dermatitis with lymphocytes and eosinophils, with superficial perivascular lymphocytic and eosinophilic infiltrate and interstitial eosinophilic infiltrate, with some eosinophils in groups located subepidermal (magnification x200).

Discussion

The particularity of this case of pemphigoid gestationis (PG) consists in the difficulties encountered in the differential diagnosis of pregnancy dermatoses that are able to modify the normal course of the pregnancy and in the atypical complication that imposed iatrogenic prematurity with short- and long-term possible modified fetal prognosis (20). Another particularity of our case were the areas affected by papules and blisters, that atypically included the face, neck, ears and scalp. Any pregnant woman presenting pruritus and skin lesions should be referred to a dermatologist and undergo the necessary investigations, along with the clinical examination of the skin and a detailed medical history. It is of high importance to establish the correct diagnosis so that the patient can receive the optimum healthcare; the evaluation of maternal and fetal prognosis is dependent on the type of dermatoses

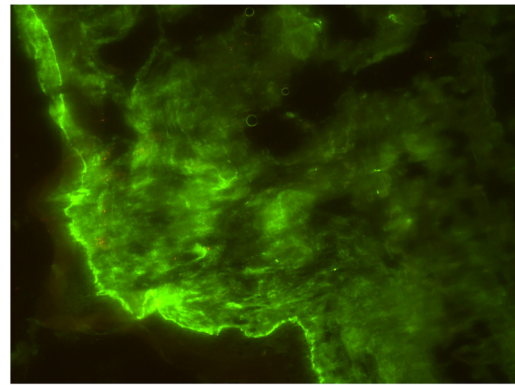


Figure 3. Direct immunofluorescence of the skin biopsy shows linear and continuous deposit of immunoglobulin G (IgG) and C3 in the dermoepidermal junction, with no IgA, IgM or C1q deposits (magnification x200).



Figure 4. Pemphigoid lesions persistent and exacerbated postpartum: blisters and plaques.

of pregnancy, as polymorphic eruption of pregnancy (5) and atopic eruption of pregnancy (4,5) do not endanger the pregnancy outcome, while pustular psoriasis of pregnancy (21,22), intrahepatic cholestasis of pregnancy (23) and PG (12) could convert the normal uneventful course of pregnancy into a high-risk pregnancy. In order to make the differential diagnosis between intrahepatic cholestasis of pregnancy and PG, the laboratory evaluation should include bile acids, prothrombin time, liver function tests and especially serum anti-BP180 antibodies (23,24). Anti-BP180 antibodies have a specificity and sensitivity between 96 and 100% for the diagnosis of PG (25). This differential diagnosis is extremely important as the first line treatment for ICP includes ursodeoxycholic acid (26) and for PG consists in topical corticosteroids (16). Furthermore, a skin biopsy, completed with a direct immunofluorescence test, should be performed to differentiate PGs from pustular psoriasis of pregnancy. These two dermatoses present different monitoring of the maternal status. For example, in PG, anti-BP180 antibodies can be used to monitor the course

of the pathology and the efficiency of the treatment (27) and in pustular psoriasis of pregnancy, a complete metabolic panel should be performed to evaluate electrolyte abnormalities, renal and liver function, possible hypoalbuminemia and the risk for hypocalcemia (22).

In our case, the diagnosis was made considering the clinical features and the result of the skin biopsy. Taking into account the positive diagnosis of PG, the monitoring of the pregnancy was modified as the clinical, blood tests and ultrasound examinations were more frequent. Although, the disease appeared in the third trimester, the fetal growth was not affected despite the intensified activity of the disease and topical and systemic corticosteroid administration. Fetal well-being status was carefully monitored by cerebro-placental ratio and nonstress tests, allowing us to detect the fetal bradycardia in good time.

Fetal myocardium and conduction tissue injury present in systemic lupus erythematosus are due to circulating antibodies to Ro (SSA) and La (SSB), which pass the placenta and affect the normal function of the fetal heart, varying from transient first-degree heart block to complete atrio-ventricular block and hydrops (28). From our knowledge, there are no studies confirming a specific effect of anti-BP180 antibodies on the fetal sinus node or whether these antibodies have a particular affinity for this tissue by a similar mechanism, which implies immune-mediated inflammatory response.

In conclusion, differential diagnosis is the first key to monitoring PG and to ensure the best maternal and fetal outcome. Additionally, there is a real need for further studies concerning the treatment standardization because being a rare cutaneous disease associated exclusively with pregnancy, there is not enough data in the literature to sustain a certain therapeutic attitude and management of this autoimmune pathology.

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Availability of data and materials

Any additional information concerning the study can be requested from the corresponding author on reasonable request.

Authors' contributions

CGP and REB conceived the concept of the article after successful management of the presented case to which IM and ADC contributed. BMM, CG and CAZ performed the literature search and wrote the draft of manuscript. CGP and DPO conducted the follow-up of the patient. IM and ADC contributed to the pathological examination of the skin biopsy. CGP, REB, BMM and CG collected, assembled and interpreted the data, making the revision of the manuscript, critically for important intellectual content. All authors have read and approved the final manuscript for publication.

Ethics approval and consent to participate

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Ethics Board of the 'Life Memorial Hospital' (Bucharest, Romania) (approval no. is 24/03.08.2021).

Patient consent for publication

The patient provided informed consent for publication of the case report.

Competing interests

The authors declare that they have no competing interests.

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